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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,972	SCHWAB ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-120 and 122-137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-120 and 122-137* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/28/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

DETAILED ACTION

1. Applicant's remarks, amendments, and sequence listing filed 28 December 2005 have been entered. Claim 121 has been canceled; claims 133 – 137 are new. Claims 114 – 120 and 122 – 137 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections and Objections

3. The following rejections or objections made in the previous office action are withdrawn:

A) The objections to claims 114 – 119 and 123 – 125 are withdrawn; applicant has canceled the offending subject matter.

B) The rejection of claims 129 – 131 under 35 USC § 112, first paragraph, for lacking enablement commensurate in scope with the claims is withdrawn in light of applicant's amendments.

C) The rejection of claims 118, 119, 122 – 124 under 35 USC § 112, first paragraph for reciting new matter. Applicant's cancellation of the material referring to residues 990 – 1178 of SEQ ID NO:29 is sufficient to overcome the rejection of claims 118 and 119. Applicant's amendments to claims 122 – 124 are sufficient to overcome the rejection.

D) The rejection of claims 115, 116, 118, 119, 123 – 125 under 35 USC § 112, second paragraph. Applicant's amendments have clarified the scope of the claims 115 – 116, 118 – 119; applicant's arguments are sufficient to overcome the rejection of claims 123 – 124.

E) The rejection of claim 127 under 35 USC 102(b) for being anticipated by Stratagene is withdrawn in light of the amendments.

F) The rejection of claims 115 – 116, 118 – 119, and 125 – 132 under 35 USC 102 for being anticipated by Bandman is withdrawn in light of the amendments.

G) The rejection of claims 115 – 116, 118 – 119, and 123 under 35 USC 102(e) for being anticipated by Machilovich is withdrawn in light of the arguments and amendments. The effective 102(e) date of Machilovich is 22 July 1999. The priority documents for the reference are foreign and thus not available for the purposes of applying prior art under 102(e).

H) The rejection of claims 118 – 119 and 123 – 125 under 35 USC 102(e) for being anticipated by Cao is withdrawn in light of the amendments.

l) The rejection of claims 126 – 128 under 35 USC 102(b) for being anticipated by GenBank AA986233 is withdrawn in light of the amendment. Claim 126, depends in part from claim 120, which requires at least 97% sequence identity. The alignment provided by applicant indicates 95% sequence identity.

J) The rejection of claim 128 under 35 USC 103 for being obvious over AA986233; AA986233 is not within the scope of the claim.

35 USC § 101

4. The claimed inventions are supported by a well-established utility. The specification discloses that the protein of SEQ ID NO:2 is rat Nogo-A (see p. 12 lines 13 – 18), that SEQ ID NO:29 is human Nogo-A (see page 15 line 11 for example) and that SEQ ID NO:32 is rat Nogo-C (see p. 8 lines 8 – 9). The Nogo-A protein is bound by monoclonal antibody IN-1 (p. 67 lines 6 – 16). Antibody IN-1 was well-known in the prior art to bind to specific myelin components (see Caroni 1988a. Neuron 1:85 –96 and Caroni 1988b Journal of Cell Biology 106:1281-1288) and permit regrowth of injured spinal cord neurons and functional recovery after lesion (see Bregman et al. 1995. Nature 378:498-501). The post-filing reference Chen et al. (2000. Nature 403:434-439) indicates that Nogo-A is the antigen bound by antibody IN-1, and that Nogo-B and –C are alternatively spliced products of the same gene. Chen teaches that rat Nogo-A protein is the protein previously described as "NI-250" (see p. 437), which served as the antigen to make IN-1 antibody (see Caroni 1988a, which teaches the creation of IN-1 antibody by immunizing mice with the 250 kD protein of myelin. On p. 86 and 95 Caroni teaches the protein is the 250 kD fraction from myelin). As the antibody IN-1 was known to be useful for treatment of nerve injury, the antigen which makes the antibody is useful.

Rejections Maintained and Necessitated by Amendment

Claim Objections

5. Claim 133 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. In the instant case, claim 133 depends from claim 127, which itself depends from claim 126. See MPEP § 608.01(n). Accordingly, the claim 133 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

6. Claims 114, 117, 120, 122 – 137 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for full-length proteins and fusions proteins which inhibit spreading of NIH3T3 fibroblasts or PC12 cells (i.e. SEQ ID NO:2, SEQ ID NO:29, residues 1 – 171 of SEQ ID NO:2 fused to residues 975 – 1163 of SEQ ID NO:2, residues 1-172 of SEQ ID NO:29 fused to residues 990-1178 of SEQ ID NO:29), does not reasonably provide enablement for those fragments claimed that do not inhibit fibroblast spreading (i.e. residues 975 – 1163 of SEQ ID NO:2, residues 990 – 1178 of SEQ ID NO:29, and SEQ ID NO:32), or for all mammalian proteins, or for all human proteins, or for all nucleic acids which hybridize under stringent conditions as defined in claim 127, or for all proteins with "Nogo activity" as broadly claimed, or for nucleic acids which encode same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons set forth in the previous office action and explained in further detail below.

The claimed invention is useful only to the extent that the proteins actually inhibit spreading of 3T3 or PC12 cells. Inhibition of cell-spreading is characteristic of myelin. Because myelin prevents the spreading of cells, it is an inhibitor of central nervous system (CNS) growth. CNS myelin is known to contain at least two substances which inhibit neurite outgrowth. These were originally identified as "NI-35" and "NI-250" and as early as 1991 were thought to be useful in guiding the pathway of developing axons, and were also thought to be useful because blocking the inhibitory properties of these molecules leads to regeneration of corticospinal tract axons (see Schwab et al. 1991. Journal of Neuroscience 11(3):709-721, particularly introductory material on p. 709.). Because the inhibitory property of the molecule is clearly what is desirable for axon guidance, where such inhibition guides the axon and keeps it on target, and is what is to be blocked when nerve regeneration is desired, this inhibitory function must be present for the claimed invention to be useful. Those embodiments which are not inhibitory (i.e. they don't prevent spreading in a fibroblast or PC12 assay) would not be expected to be useful in any therapeutic setting and thus are inoperative.

On p. 14 – 15 of the remarks filed 28 December 2005, applicant cites several cases as forming the legal basis of the enablement standard. Applicant is correct that these cases provide insight into the courts' interpretations of the enablement standard over the past 35 years. However the selective citation of passages from the various cases obscures the findings

in the cases. Applicant also cites MPEP § 2164.01(c) in a selective fashion. The quoted section, as well as the sentences immediately preceding it, are reproduced below:

> "...[W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." (emphasis added)

Claims 114, 117, 120, 122, 125 – 132, and 135 encompass fragments of the disclosed proteins which are inoperative. The entire scope of the relevant claims include full-length Nogo proteins, identified by SEQ ID NO:, as well as specific fragments which are known to be inoperative. The specific inoperative fragments are residues 975 – 1163 of SEQ ID NO:2 and residues 990 – 1178 of SEQ ID NO:29, as well as the entirety of SEQ ID NO:32. As set forth in the previous office action, applicant's disclosure indicates that these fragments, when tested in the PC12 cell neurite assay, do not inhibit the spreading of neurites. Thus they lack the activity which is crucial for the proteins. Applicant argues, on p. 16 of the remarks, that the fragments which are disclosed to be inactive are in fact useful because they can be used to generate antibodies. Applicant's arguments have been fully considered but are not persuasive. Hopp et al. (1981. Proc Natl Acad Sci. USA 78:3824-3828, cited by applicant on IDS filed 28 December 2005) teach that any six consecutive amino acids are antigenic and can be used to produce antibodies. Thus applicant's recitation of inactive fragments does not distinguish those fragments over the plethora of other inactive fragments contained within the full-length proteins.

The specification discloses that the "invention also relates to Nogo derivatives and analogs of the invention which are functionally active, i.e. they are capable of displaying one more known functional activities associated with a naturally occurring Nogo protein. ... Such functional activities include ... neurite growth inhibition... immunogenicity which is the ability to generate antibody which binds to Nogo. These antibodies having the potential to induce neurite outgrowth... by inhibiting the function of Nogo" (specification, p. 3, second paragraph). Clearly applicant has conceived that the antibodies are useful in that they prevent the activity of the protein, i.e. by binding to those regions know to be active. So using the inactive regions of the

protein would produce antibodies which would not be expected to have the activity disclosed in the specification. The protein fragments themselves are not useful for preventing neurite outgrowth, and they could not reasonably be used to generate antibodies which inhibit Nogo activity, as the antibodies would be directed at inactive fragments. The examiner notes that this aspect of the scope of enablement rejection could be overcome if applicant were to amend the claims such that fragments without neurite-inhibiting activity were no longer claimed.

Claims 115 – 116, 118 – 119 all recite the limitation "wherein said protein has Nogo activity". This term is defined in a very broad manner in the specification. The specification discloses that the activities associated with full-length wild-type Nogo protein include such elements as antigenicity and immunogenicity as well as the ability to inhibit spreading of NIH 3T3 cells *in vitro* (see p. 11 lines 20 – 30). However, the specification does not disclose to the artisan how to use those portions of Nogo protein which are antigenic or immunogenic but non-functional. Applicant argues that these fragments could be used to make antibodies, and thus are useful. Since the art recognized that the utility of antibodies such as IN-1 is that they prevent Nogo protein (also called NI-250) from exerting its inhibitory action, antibodies which are raised against non-inhibitory fragments (such as residues 975 – 1163 of SEQ ID NO:2, residues 990 – 1178 of SEQ ID NO:29, and SEQ ID NO:32) would not be expected to be useful. The specification does not teach the artisan how to use the fragments how to use non-inhibitory fragments or variants of the protein, so the artisan would essentially have to discover how to use them on his own. Such a requirement for experimentation is not routine, and would be undue. Thus claims to proteins what have "Nogo activity" as broadly defined are not enabled commensurate in their scope. While the discussion above is on point to proteins, the same logic applies to the nucleic acids claimed herein, as they are to be used for recombinant production of protein (see for example claim 132)

Claim 126 is drawn to any isolated nucleic acid which encodes a protein of any one of claims 114 – 120 or 122. As the protein claims are not enabled over their full scope for the reasons set forth above, the same is necessarily true for the nucleic acids. While claim 127 has been amended to recite specific washing conditions, it still ultimately depends from several non-enabled claims and thus is rejected as well; similarly claims 128 – 133 are rejected.

Claims 134 – 137 are new and each recite a large number of protein fragments. Like the previously presented claims, these claims each recite a number of embodiments which, through applicant's careful testing, have been shown to be inactive. The results of the experiments

which appear on p. 68 of the specification clearly indicate which fragments are useful as determined by the neurite outgrowth assays, and which do not work. The list spanning p. 9 – 10 of the specification provides the exact amino acid residue numbers that correspond to the named fragments on page 68. Applicant has determined that the region from residues 172 – 259 and from 975 – 1162, using the numbering scheme of SEQ ID NO:2, do not work and can be deleted without the loss of inhibitory activity. Yet applicant insists on claiming these non-functioning embodiments. For example, claim 134, part (vi), and claim 135, part (xv), each recite residues 172 – 259 of SEQ ID NO:2. Claim 135, part (xviii) recites residues 975 – 1162 of SEQ ID NO:2. Additionally, claim 134, part (v), (viii), (ix), as well as claim 135, part (i), (ii), (iv) – (xiv), (xvi) – (xvii) encompass fragments which are not even listed in this assay. There is no evidence that they are functional, and since the functional fragments have been carefully set forth in the specification, a skilled artisan would conclude it is more likely than not that the fragments listed in claim 134 parts (v), (viii), and (ix), and in claim 135, part (i), (ii), (iv) – (xiv), (xvi) – (xvii) are not functional. Claims 134 – 135 do not require that protein fragments have any particular activity. It appears that once again applicant is attempting to claim useless fragments, as they could not be used for therapy, or as targets for therapy, or for generation of antibodies which could then be used for therapy. Similarly, claims 136 - 137, parts (vii) is drawn to a protein fragment which is not required to have any activity, but only has to be at least 95% identical to a fragment homologous to a non-functional portion of the protein. If applicant were to amend the claims to those embodiments which have actually been demonstrated to be useful, the rejections could be obviated to the extent that they include non-enabled embodiments. However, because applicant is claiming those fragments which do not work, as well as proteins comprising the fragments, and proteins related by sequence identity to non-functional embodiments, the rejection for lack of enablement commensurate in scope with the claims is maintained.

7. Claims 115 – 116, 118 – 119, 122 – 134, and 136 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained for the reasons set forth in the previous office action and explained in further detail below. Claims 115 – 116, 118 – 119, 122, 134, and 136 are genus claims. The claims encompass not only the disclosed sequences recited in the claims, but also encompass those sequences which are related by percentage identity. Applicant cites, beginning on p. 21 of the remarks, several cases which form the basis of the current interpretation of the written description requirement. Applicant also cites the Guidelines issued by the Office.

Applicant's arguments have been fully considered but are not persuasive. Of course what is well-known in the art need not be disclosed in the specification. The specification has defined "Nogo activity" very broadly. Functional activities of Nogo are set forth on p. 11, lines 20 – 30, and include such features as ability to restrict growth or spreading of neurites in vitro, but also include such features as antigenicity and immunogenicity. While the data presented on p. 68 of the specification, in combination with the corresponding list of constructs set forth on p. 10 and Figure 18, do show which regions of the proteins are important for imparting the neurite-outgrowth-inhibitor activity, they do not in fact show which regions are required for the full genus of Nogo activity as claimed.

Furthermore the specification does not disclose a representative number of the genus of proteins at least 90% identical to the protein which has residues 1 – 171 of SEQ ID NO:2 fused to residues 975 – 1163 of SEQ ID NO:2, which is recited in claim 115. The only member of said genus disclosed is that protein which is identical to that fusion protein. As the written description component of 35 USC § 112, first paragraph, requires that the specification show that the inventor had possession of the claimed genus (see remarks filed 28 December 2005, p. 22, citing the Federal Register Vol. 66), and this specification clearly falls short with respect to that standard, those claims that encompass genera stand rejected.

Applicant argues, on p. 23 of the remarks, that the enclosure of a hydrophobicity analysis using Hopp and Woods' amino acid scale is sufficient to show possession of the entire genus claimed. Applicant's arguments have been fully considered but are not persuasive. The analysis performed is not sufficient to show applicant was in possession of the genera claimed. Claims 115 – 116, 118 – 119 all require that the protein have Nogo activity. Since this activity has been defined by applicant as including the ability to inhibit spreading in the NIH3T3 assay, and as set forth in the rejection for lack of enablement commensurate in scope with the claims this is the only reasonable use for the claimed invention, the discussion of immunogenicity does

not appear to be germane. In order to show possession of the very broad genus claimed, either the specification or the prior art must disclose those structural elements which impart the function. There is not a structure common to all members of the genus of proteins which are antigenic.

Applicant argues, on p. 24 of the remarks, that the amendments to claims 123 – 124 is sufficient to overcome the rejection for lack of written description. The examiner disagrees. Claim 123 depends from claims 115 – 116 and 119; as those claims are all genus claims and are rejected for the reasons set forth above, claim 123 remains rejected. Applicant has not disclosed which features of those proteins at least 90% – 95% identical to the disclosed proteins are required to make the proteins mammalian. Similarly, applicant has not disclosed which features of those proteins claimed in claims 118, 119, or 122 (from which claim 124 depends) are required to make them human.

Applicant's amendment to claim 127 is sufficient to overcome the rejection with respect to its reading on an unlimited number of sequences because no washing step was recited. However as the claim depends from rejected base and intermediate claims, it stands rejected.

8. Claims 117 and 125 - 136 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 117 was rejected in the previous office action for reciting residues 990 – 1178 of SEQ ID NO:29. Applicant has canceled this recitation, but has added the recitation "the carboxy-terminal 188 amino acids of SEQ ID NO:29". Applicant argues, on pp. 24 – 25 of the remarks, that support for this limitation can be found on p. 12, lines 21 – 26 of the specification. The examiner is able to find support for "the carboxy terminal 188 amino acids of Nogo A" discussed in the context of a fusion protein encoded by certain nucleic acids. However Nogo A is not disclosed as being identical to SEQ ID NO:29; SEQ ID NO:29 is human Nogo. Furthermore Figure 13 indicates that human Nogo and rat Nogo A differ in the carboxy terminal region, including at residues 1121 and 1171, using the numbering system on Figure 13. The examiner cannot find *ipsis verbis* support for the newly-added limitation. Claims 125 – 133 each depend from claim 117, and thus stand rejected for the same reasons.

New claims 134 – 136 encompass several polypeptides and variants of polypeptides which do not find sufficient support in the specification, drawings, or claims as originally filed. On p. 13 of the remarks, applicant directs the examiner's attention to specific pages and lines of the specification as providing support for the newly-added claims. After careful consideration of the cited regions, the examiner is unable to find support for the following elements:

1) Claim 134, as a whole. There does not appear to be either disclosure of, or even contemplation of, fragments at least 95% identical to the residues recited in claim 134. While fragments are listed, for example on pp. 10 and 17 of the specification as originally filed, these fragments are not mentioned in the context of fragments at least 95% identical to other proteins, but rather within the context of functional analysis of Nogo by deleting certain nucleic acid bases. Applicant did not contemplate fragments at least 95% identical to the recited residues of SEQ ID NO:2 at the time of filing. Additionally the examiner is unable to find support for the specific fragment recited in element (ix) of the claim, that is, residues 623 – 640.

2) Claim 135. The examiner is unable to find support in the original claims, specification, and drawings for the following fragments: residues 31 – 57 of SEQ ID NO:2, 11 – 191 of SEQ ID NO:32, residues 1090 – 1125 of SEQ ID NO:2, residues 623 – 640 of SEQ ID NO:2.

3) Claim 136. Applicant notes in the remarks filed 28 December 2005 (p. 13, footnotes) that the specification was amended on 21 October 2002 to change the sequence identifiers from SEQ ID NO:30 to SEQ ID NO:29. The examiner concedes that such modification appears to have been appropriate, as that date is the first date a computer-readable sequence was filed. However, there does not appear to be either disclosure of, or even contemplation of, fragments at least 95% identical to the residues recited in claim 136. While fragments are listed, for example on pp. 10 and 17 of the specification as originally filed, these fragments are not mentioned in the context of fragments at least 95% identical to other proteins, but rather within the context of functional analysis of Nogo by deleting certain nucleic acid bases. Applicant did not contemplate fragments at least 95% identical to the recited residues of SEQ ID NO:29 at the time of filing.

Thus, the newly-presented limitations set forth above constitute new matter.

9. Claim 127 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. This rejection is maintained for the reasons made of record in the previous office action.

Applicant argues that since many other U.S. patents have issued with the word "Ficoll" recited in the claims, the examiner should disregard the second paragraph of § 112 and permit the recitation of the term in this case. Furthermore applicant argues that MPEP § 2173.05(u) permits the inclusion terms which are commonly used in claims, whether or not they are trademarked. Applicant's arguments have been fully considered but they are not persuasive. MPEP § 2173.05(u) is quite clear on the matter:

> If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name. (emphasis added)

Here, the word Ficoll is used to identify the product known generically as thiocyclam hydrogen oxalate (see attached printout from Sigma website). Thus according to MPEP § 2173.05(u), the scope of the claim is uncertain and the claim does not comply with § 112, second paragraph. This rejection could be overcome by amending the claim to recite the generic, rather than trademarked, name.

Priority

10. On p. 28 of the remarks applicant argues that the effective filing date of all claims is 6 November 1998. Claim 117 and new claims 134 – 136 recite new matter, as set forth in the rejection under 35 USC § 112, first paragraph, above. Thus the effective filing date for the purposes of applying prior art for claims 117 and 134 – 136 is the filing date of the instant application, namely 24 September 2001. Claim 125 – 133 each depend from claim 117 and thus the effective filing date of those claims is also 24 September 2001. The effective filing date of claims 114 – 116, 118 – 120, 122 – 124, and 137 is the date the provisional application was filed, 6 November 1998.

Claim Rejections - 35 USC § 102

11. Claims 117, 125 – 132 are rejected under 35 U.S.C. 102(e) as being anticipated by Michalovich et al. (US Patent Application Publication 2002/0010324, published 24 January 2002, effective filing date 22 July 1999).

On p. 32 of the remarks, applicant argues that the publication by Michalovich is not available as prior art because the earliest effective date of the reference is 22 July 1999. Applicant is correct that foreign priority dates are not to be relied upon; the examiner concedes the reference is only available as of 22 July 1999. However, as claims 117 and 125 – 132 are only entitled to 24 September 2001 as their effective filing date for the reasons set forth above, the Michalovich reference is still effective against those claims. As set forth on p. 10 of the previous office action, Michalovich teaches SEQ ID NO:2, and the 188 C-terminal residues of applicant's SEQ ID NO:29 are identical to the prior art sequence. Thus the reference anticipates claim 117 and 125 – 132 for the reasons of record.

12. Claims 117, 125 – 127, 134 - 135 are rejected under 35 U.S.C. 102(e) as being anticipated by Eiesenbach-Schwartz et al. (U.S. Patent Application Publication 2002/0072493 published 13 June 2002, filed 28 June 2001).

This rejection is maintained for the reasons of record. Applicant argues, on p. 33 of the remarks, that the reference is not prior art. The examiner concedes that the effective filing date of the reference by Eisenbach-Schwartz is 28 June 2001. However for the reasons set forth above, the effective filing date of claims 117 and 125 – 127 is 24 September 2001 and thus Eisenbach-Schwartz anticipates these claims.

New claim 134 encompasses a fragment of the protein; Eisenbach-Schwartz teach SEQ ID NO:19 which is an 18 amino acid fragment. This fragment is identical to residues 623 – 640 of applicant's SEQ ID NO:2 and thus meets the limitation of claim 134, part ix and claim 135, part viii. As set forth above, these claims are only entitled to 24 September 2001 as the effective filing date.

13. Claims 126 – 127 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank AF132047, publicly available on 18 May 1999.

This rejection is maintained for the reasons of record. Applicant argues, on p. 34 of the remarks, that these claims are entitled to 6 November 1999 as a priority date. For the reasons set forth above, the claims are only entitled to the instant filing date, namely 24 September 2001. Applicant did not traverse the examiner's reasoning, so the same reasoning applies as was set forth previously.

14. Claims 126 and 127 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank AB015639, publicly available on 3 September 1999.

This rejection is maintained for the reasons of record. Applicant argues, on p. 34 of the remarks, that these claims are entitled to 6 November 1999 as a priority date. For the reasons set forth above, the claims are only entitled to the instant filing date, namely 24 September 2001. Applicant did not traverse the examiner's reasoning, so the same reasoning applies as was set forth previously.

Claim Rejections - 35 USC § 103

15. Claims 128 – 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of GenBank loci AF132047 or AB015639 or Eisenbach-Schwartz et al., each in view of Schendel 1998. Current Protocols in Molecular Biology 16.1.1 – 16.1.3).

This rejection is maintained for the reasons of record. Applicant argues, on p. 35 of the remarks, that AF132047, AB015639, and Eisenbach-Schwartz are not prior art and cannot properly form the basis of a rejection under § 103. However for the reasons set forth previously, claims 128 – 132 are not entitled to the earlier filing date, and thus the rejections stand for the reasons of record.

New Rejections

Claim Rejections - 35 USC § 102

16. Claims 114, 116, 123, 125 are rejected under 35 U.S.C. 102(b) as being anticipated by Caroni (1988b Journal of Cell Biology 106:1281-1288) as evidenced by Chen (2000. Nature 403:434-439) and Caroni (1988a Neuron 1:85-96).

These claims encompass the protein of SEQ ID NO:2. The specification discloses that SEQ ID NO:2 is rat Nogo-A (see p. 12 lines 13 – 18). Caroni teaches isolation of proteins from rat myelin. The specific methods used to ensure that the proteins are free of all CNS myelin

with which they are natively associated are set forth on p. 1282, second column. The proteins were isolated on SDS-PAGE gels, and various bands were cut out from the gels and tested for their ability to inhibit spreading in the 3T3 assay (see p. 1285). Caroni teaches that two specific bands, those with molecular weights of 35 and 210 respectively, account for most of the inhibitory activity. However Caroni is silent as to the identity of these proteins.

Chen teaches isolation of nucleic acids encoding rat Nogo-A protein. Chen teaches that Nogo-A protein has many of the same properties as "NI-250" protein and that it "probably corresponds to rat NI-250 (see end of p. 434). NI-250 is the 250-kD protein that was isolated by Caroni (1988b). Caroni (1988a) teaches that IN-1 is the antibody raised against the 250kD protein (see p. 86). Chen teaches that the IN-1 antigen and Nogo-A both are present in CNS myelin, and antisera again Nogo-A reproduce the effects of IN-1 (see Chen p. 437). Chen even offers an explanation for the apparent discrepancy between the observed molecular weight of rat NI-250 and recombinant Nogo-A; he attributes the difference to glycosylation and different gel-running procedures (p. 437, second column). Finally, Chen discloses that the amino acid sequence of Nogo-A is 1163 residues long and has been deposited as accession number AJ242961 (see p. 434). The attached printouts indicate that this accession number encodes the protein of SEQ ID NO:2. Thus the reference by Chen provides evidence that the 250-kD protein isolated by Caroni (1988b) is the same as the protein of SEQ ID NO:2 and anticipates claims 114 and 126. As the protein is mammalian, it meets the limitations of claim 123. Claim 125 requires that the protein be recombinant, however this is a product-by-process limitation which does not distinguish the claimed invention from the prior art product.

17. Claims 117 – 119, 123 – 125, and 136 – 137 are rejected under 35 U.S.C. 102(b) as being anticipated by Spillman (March 1997. European Journal of Neuroscience 9:549-555), as evidenced by Chen (2000. Nature 403:434-439).

The claims encompass the protein of SEQ ID NO:29, which is disclosed as being human Nogo-A protein. Spillman teaches isolation of a high molecular weight protein from human myelin. Human myelin was obtained from post-mortem tissue, and the proteins were isolated with CHAPS buffer and then separated on an SDS gel (see p. 550). The protein from several regions of the gel were cut out and used in experiments to determine their ability to inhibit neurite outgrowth of PC12 cells. The data presented in Figure 3 indicate that the fraction from 200-300 kD in weight was most effective in this inhibition. Furthermore the inhibition could be

blocked by antibody IN-1, which is the antibody that binds to rat Nogo-A (see Chen). Spillman teaches that the human fraction contains a protein of the same size and with the same properties as the rat 250 kD protein which was later shown by Chen to be Nogo-A. Spillman also teaches that since the human protein's effects can be neutralized by IN-1 antibody, there is a highly conserved epitope between the human and rat proteins. While Spillman is silent as to the sequence of the protein, this is a property of the protein and cannot be separated from the product. Thus as Spillman teaches isolation of the protein which a) has a similar molecular weight, b) has similar Nogo activity (inhibition of neurite outgrowth in PC12 cell assay) and c) binds the same antibody that binds rat Nogo-A, the prior art protein is indistinguishable from the protein of SEQ ID NO:29 and thus anticipates claims 117 – 119. Claims 123 – 124 are drawn to mammalian and human proteins respectively; as the Spillman reference teaches the protein was isolated from human tissue, it meets these limitations. Claim 125 requires that the protein be recombinant, however this is a product-by-process limitation which does not distinguish the claimed invention from the prior art product.

Claims 136 – 137 depend from rejected claim 118. The claims do not require that the fragments be of any particular length, only that they comprise certain specific residues of SEQ ID NO:29. As the protein disclosed by Spillman is the full-length protein of SEQ ID NO:29, it includes all the fragments recited in claims 136 - 137.

After setting forth a prima facie case of inherency, the burden shifts to applicant to distinguish the claimed invention from the prior art (see MPEP § 2112(V)).

18. Claims 114 – 116, 120, 122 – 123, 125, 134 – 135 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Caroni (1988a), Caroni (1988b).

Claims 114 – 116 encompass residues 1 – 171 fused to residues 975 – 1162 of SEQ ID NO:2, claims 120 and 122 encompass SEQ ID NO:29. The specification discloses that rat Nogo-B is residues 1 – 171 fused to residues 975 – 1162 of SEQ ID NO:2 and that rat Nogo-C is residues 975 – 1162 of SEQ ID NO:2 (see for example p. 10 line 1). Rat Nogo C is also disclosed as being the first 11 amino acids of SEQ ID NO:2 fused to the C-terminal 188 amino acid residues of the same protein (specification p. 12 lines 24 – 28). Rat Nogo C sequence is set forth in SEQ ID NO:29. Rat Nogo B and C arise from the same gene as rat Nogo A but are alternatively spliced or transcribed variants (specification, p. 12). Thus they share at least the

same carboxy-terminal 188 residues with Nogo A protein and both Nogo-B and Nogo-C would be expected to be smaller than Nogo-A on a gel.

Caroni 1988b teaches isolation of two proteins from rat myelin with inhibitory activity in the 3T3 spreading assay. The proteins have molecular weights of 250 kD and 35 kD respectively. As set forth in the rejection under 102(b) above, the 250 kD protein is Nogo-A. Caroni 1988a teaches that antibody IN-1 binds to, and negates the inhibitory effects of, both the 250- and 35-kD protein. The 35 kD protein appears to be either Nogo B protein or Nogo C protein. It is bound by the same antibodies that bind to rat Nogo-A and therefore shares considerable sequence identity with this molecule, and is much smaller than the 250 kD protein. The USPTO does not have the resources to determine if the prior art protein has the sequence set forth as residues 1 – 171 fused to residues 975 – 1162 of SEQ ID NO:2 or as SEQ ID NO:32. As the prior art product (35 kD inhibitory protein) has many of the same features as both Nogo-B and Nogo-C, the examiner cannot determine which properties such as the sequences are inherent to the prior art product.

Claims 134 – 135 depend form rejected claim 115. The claims do not require that the fragments be of any particular length, only that they comprise certain specific residues of SEQ ID NO:2. As the protein disclosed by Spillman is not distinguishable from Nogo B (residues 1 – 171 of SEQ ID NO:2 fused to residues 975 – 1163 of SEQ ID NO:2), it includes all the fragments recited in claims 134 – 135.

Claim 127 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen (1997. Society for Neuroscience Abstracts 23:1723. Abstract presented at 27th Annual Meeting of the Society for Neuroscience, 25 – 30 October 1997) and evidenced by Chen (2000).

Chen (1997) teaches isolation of cDNAs encoding the rat protein bound by antibody IN-1. Chen teaches possession of two rat cDNA sequences, called Oli18 and EST. The reference teaches isolation of three different RNA transcripts on Northern blots, each of which is an alternatively spliced variant of the same gene. Chen (1997) is silent as to the sequences of the isolated nucleic acids but teaches that they are 2kb, 3kb, and 5kb in size respectively.

Chen (2000) teaches rat Nogo nucleic acids. The nucleic acids encode Nogo proteins and are alternatively spliced variants of the same gene. Chen (2000) teaches that Nogo-A protein is identical to NI-250 protein, and teaches that the protein is bound by IN-1 antibody. Furthermore Chen (2000) teaches that Northern blots for Nogo nucleic acid reveal three isolated

nucleic acids, which are 1.7, 2.6, and 4.6 kb in length. The prior art products from Chen (1997) are indistinguishable from the invention recited in claims 127 and 132.

Claim Rejections - 35 USC § 103

Claims 127 – 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (1997. Society for Neuroscience Abstracts 23:1723) and Sambrook (1989. Molecular Cloning, pp. 16.3 – 16.22 and 17.3 – 17.9) and Bregman et al. (1995. Nature 378:498-501).

The reasons why Chen 1997 anticipates claim 127 are set forth in the rejection under 35 USC 102(b) above. However Chen does not teach nucleic acids in vectors, or host cells comprising said nucleic acids, or methods of making protein recombinantly. Sambrook teaches methods of making protein recombinantly, using *E. coli* as the host cell and teaches vectors which are suitable for such purposes (see text excerpted from chapter 17) and also teaches similar methods with eukaryotic cells (see text from chapter 16). It would have been obvious to one of ordinary skill in the art to insert the nucleic acids of Chen into vectors, put those vectors in host cells, and make protein from the host cells, as taught by Sambrook, with a reasonable expectation of success. A motivation to do so would be to produce large quantities of the protein, which is then useful for making antibodies for therapeutic use, as Bregman teaches such antibodies are suitable for recovery from nerve injury at both the anatomical and functional levels.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
4/3/06

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-31-06

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OM protein - nucleic search, using frame_plus_p2n model

Run on: April 16, 2005, 11:30:21 ; Search time 14217.1 Seconds
(without alignments)
3963.787 Million cell updates/sec

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Searched: 4708233 seqs, 24227607955 residues

Total number of hits satisfying chosen parameters: 9416466

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Post-processing: Minimum Match 0%
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Listing first 45 summaries

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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	5	5307	90.7	3821	10	AY114152	AY114152 Mus muscu
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	27	3714	63.5	4123	9	AY123247	AY123247 Homo sapi
	28	3711	63.5	4160	9	AY123246	AY123246 Homo sapi
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